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EXAMINER	
DHRUVA, B	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/586,535	AUDONNET ET AL.	
	Examiner	Art Unit	
	Bharati R. Dhruva	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-11 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-11 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED ACTION

Objection

The claims are objected to because they lack a proper introduction, which appears as 'CLAIMS" at the top of the page 30. The present Office practice is to insist that each claim must be the object of the sentence starting with "I or (We) claim", "The invention claimed is" or the equivalent. MPEP 608.01(m).

On page 3 line 19 the parenthesis is open. It should be closed or removed.
On page 21 line 25 the specification describes the concentration of DNA to be at 250ug/ul. Should this be ug/ml as it is earlier on line 8 and later on page 24 (line 21-22) described?

Page 30 line 20 has a spelling mistake. " ou " instead of "or".
The applicants are advised to check the document for additional mistakes and correct it without adding new matter. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is unclear and vague. The claim is unclear and vague because the phrase " comprising on one hand" and "on the other hand " is not clear. What is meant

by one hand and the other hand. It is not clear if the elements must be included or are optional. The metes and bound of the claim can not be determined.

In claim 2-11 the phrase "characterized in that " is unclear and vague. At what level of immune enhancement the elements are deemed to be characterized as the elements which increases the immune response.

Claim 11 fails to point out which porcine immunogen will be used. The term "another" is vague and indefinite. It fails to specify if the immunogen is from part of porcine circoviirus or any other source. If it is from the porcine circovirus, which of the four open reading frames of the viral genome, in addition to the ORF1 and 2 used in the present invention, is immunogenic? What other immunogens will be used? Are they known or unknown?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for immunogenic preparation of ORFs 1 and 2 of Porcine circovirus-2 (PCV-2) and of PCV-1, with DMRIE and DOPE and GM-CSF does not reasonably provide enablement for an immunogenic preparation of ORFs 1 and 2 with carbomer or for immunogenic preparation with any other porcine immunogen in presence of DMRIE/DOPE, carbomer or porcine GM-CSF. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-11 are drawn to an immunogenic preparation or a vaccine comprising plasmid encoding and expressing a gene selected from the group consisting of ORF1 of PCV-2 , ORF2 of PCV-2 , ORF1 of PCV-1 , ORF2 of PCV-1 and an element capable of increasing the immune response directed against the product of expression of the gene. The claims further define the elements to be cationic lipids DMRIE/DOPE, carbomer or plasmid expressing porcine GM-CSF.

Restifo and Babiuk (Gene Therapy, 2000, Vol. 7, page 89-92 and Veterinary immunology and Immunopathology, Vol. 76, pp. 1-23) discuss the great potential for DNA vaccines and the numerous obstacles to overcome before it can be exploited for vaccination purpose. Although, the DNA vaccination stimulates both cellular and humoral immune response resembling closely the natural immune responses, the immunization with DNA vaccine is inefficient (Restifo page 89 para.2). The greatest challenge to nucleotide vaccination observed is the lack of efficient delivery system. So far DNA has been delivered to cells *in vivo* by (1) mechanical, (2) electrical and (3) chemical mean. These routes have multistep process, cell entry, migration through cytoplasm and entry into nucleus, leading to possibility of DNA degradation (Babuik et al. page 14 line 1-12). Babiuk et al. also discuss the dramatic influence of route of delivery, intramuscular verses intradermal and the method of delivery naked DNA or the liposome-DNA complex, on immune response (pp. 3 para.2- and page 4). The

vaccination by naked DNA requires high concentration of DNA and so far only intradermal injections have elicited immune response at low DNA concentrations (Babuik et al. page 3 para.4). Babuik et al. suggest that improvement of transfection efficiency and expression of antigen in dendritic cells should be one of the targets of research for improving efficacy of DNA immunization (pp.4 lines 3-4). Yokoyama et al. (FEMS Immunology and medical microbiology, 1996, Vol. 14,pp.221-230) reported that there is marked effect on immune response based on route of delivery and vehicle of the delivery (pp. 228 para.2) Furthermore they report that these effect are unpredictable since a particular vehicle would be beneficial in one route and but inhibitory in another route, for example cationic lipids enhance expression following intravenous administrations but markedly reduce expression following intramuscular injections (pp.228, 2nd column, lines 3-9).

The specification describe intramuscular immunization of the new borne and 14 day old piglets, injected with an immunogenic preparation of plasmids expressing ORF1 or ORF 1and 2 together with or without cationic lipids and challenges the piglets by virus introduced through intranasl or oral route (page 21-27 Example. 10). The specification determines the protective immune response to PCV challenge by determining the lymphoadenopathy, viral load in lymph node and shedding of virus in fecal material.

The specification only teaches use of ORF 1 and ORF 2 of the PCV-2. There is no evidence in the specification or in the prior art that any of the other four ORFs of the porcine circovirus genome would give protective immunity to the vaccinated animals.

The specification does not discuss any other porcine immunogen to be delivered by the present method. It is well know in the art that any foreign protein can generate immune response but may not provide protective immunity. The specification does not provide any direction for which immunogens will be used.

Although the claim encompasses carbomer as the element, to increases immune response, there is no evidence within the specification that this compound together with plasmids expressing the ORFs of PCV enhanced immune response. Carbomer with influenza HA vaccine was reported to enhance the immune response in horses (Mumford et al. 1994, Epidemiology and Infection, Vol. 112, 421-437; pp.421 abstract and pp.423 Table 1). The specification or the prior art do not teach the use of carbomer as immune enhancer with DNA vaccines, furthermore they do not teach the concentration and the time of administration, prior to, with or following injection of DNA lipid complex, for carbomer administration.

The prior art does teach the use of plasmid expressing GM-CSF together with DNA vaccine (Restifo et al. pp.90, para 6, and lines 18-20, Okada et al. Fig. 4 and 5, page 3641 para.2 lines 9-11). It is known that GM-CSF can stimulate the growth and differentiation of various progenitor cells and hence can influence both humoral and cellular immune response. GM-CSF also have been thought to recruit and mature dendritic cells. Therefore, it would enhance the efficacy of the DNA vaccines and would be part of a composition.

Though there are large number of genetic vaccine-studies, the results are inconsistent and difficult to compare. Number of factors influence the immunogencity of

the DNA vaccine; structure of plasmid backbone e.g. presence of CpG dinucleotide sequences, intron etc.; the amount of plasmid delivered, expression level of the antigen, immunization schedule, route of immunization, target tissue, number of immunization, method of immunization intramuscular, intradermal; age of the subject, strain of the particular species of mice and toxicity of the antigen (Leitner et al. pp.767, Table1). Yokoyama et al. teach that in their studies only intravenous injection of DNA complexed with cationic lipid show increase in antibody level in mice

While applicants do not need to provide evidence for selection of other porcine immunogen which would provide treatment for various porcine diseases, in view of the factors discussed above such as, DNA backbone and sequence of the plasmid, the route of delivery and the composition of the DNA vaccine, which influence the immune response, the demonstration of protective immunity with porcine circovirus ORFs 1 and 2 are insufficient evidence for enablement for any and all porcine immunogens delivered by any route to generate prophylactic or therapeutic immune response against any pathogenic agent. It would require undue experimentation for a skilled artisan to select immunogens, composition and route of delivery for an effective outcome of the DNA vaccination.

Furthermore, the lack guidance in the specification and the lack of teaching in the prior art on use of carbomer with DNA vaccine, it would also require undue experimentation to determine the concentration, time of administration of carbomer and the best route of delivery.

Thus the claimed invention, in view of the prior art and the teaching in the specification, is limited in scope to an immunogenic preparation, for protection of porcine circovirus infection in pig, delivered by intramuscular and intradermal route, comprising plasmids expressing ORF1 and ORF 2 of PCV-2 and PCV-1, a plasmid encoding porcine GM-CSF, mixed with cationic lipids DMRIE/DOPE.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 (b) that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim1 and 7-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Okada et al. (Journal of Immunology, 1997, Vol. 159, pp.3638-3647) .

Claim 1 is drawn to an immunogenic preparation or vaccine comprising *on the one hand,* a plasmid encoding and expressing a gene selected from the group consisting ORF1 of PCV-2, ORF2 of PCV-2, ORF1 of PCV-1, ORF2 of PCV-1 and *on other hand*, an element capable of increasing the immune response directed against the product of expression of the gene. Claims 7-9 further limit the elements capable of increasing the immune response to be porcine GM-CSF(see 112, 2nd para. Rejection).

Okada et teach an immunogenic preparation comprising plasmids pCMV160IIIB expressing HIV *env*, pcREV expressing full length regulatory *rev* and a plasmid encoding and expressing mouse GM-CSF (page 3639 para.3, lines 4--7 and para.4, lines 11-13 and Figures 4 and 5).

As such the immunogenic preparation taught by Okada et al. meet the limitation of the claim. Hence the invention is anticipated by Okada et al.

Claims 1 and 11 are rejected under 35 U.S.C. 102b as being anticipated by Meehan et al. (Journal of general Virology, 1998, Vol.79, pp.2171-2179).

Claim 1 and dependent claim 11 recite a vaccine preparation comprising on the one hand a plasmid encoding and expressing a gene expressing a gene selected from the group consisting of ORF 1 of PCV -2, ORF 2 of PCV -2, ORF 1 of PCV -1 and ORF 2 of PCV -2, and on the other hand an element capable of increasing the immune response directed against the product of the gene expression.

Meehan et al teach a plasmid, which comprises the ORF 1 and 2 of Porcine cirocovirus-2 and PCV-1. (pp. 2172, para. 7, lines 5-8 and para.5, lines 1-3 respectively). Furthermore there is a striking difference in the protein sequences encoded by PCV-1 and PCV-2(Imp.1010-stoon EcoRI no.14) indicating that antigenically these two viruses are distinct (pp.2178, para 1.complete). Furthermore, the other ORFs of PCV-1 and 2 beside the ORF1 and 2 can be used as other porcine immunogen.

Meehan et al anticipate claims, 1 and 11, hence the invention is anticipated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meehan et al. (Journal of general Virology, 1998, Vol.79, pp.2171-2179).in view of Okada et al. (Journal of Immunology, 1997, Vol. 159, pp.3638-3647).

Claim 1 is drawn to an immunogenic preparation, comprising a plasmid expressing a gene selected from the group consisting of ORF 1 of PCV -2, ORF 2 of PCV -2, ORF 1 of PCV -1 and ORF 2 of PCV -2, and an element capable of increasing the immune response directed against the product of the gene expression.

Claim 11, further encompasses a plasmid encoding another porcine immunogen.

Meehan et al. teach isolation, cloning and sequence analysis of porcine circovirus (PCV) which causes wasting syndrome in pigs and compare it to the PCV-PK (page 2172 , complete and 2175 para.6) a tissue culture isolate of the virus from PK-12 cell line. Based on sequence analysis, they identified six open reading frames (Fig. 4) and describe potential involvement of ORF 1 in virus replication (page 2176, para.3 and page 2177 para.1, lines 6,) and of the other ORFs in structural proteins (page 2177,

para.5, lines 5-7). Meehan et al. do not teach a immunogenic composition comprising the plasmid encodingORF1 and 2 of PCV-2 and PCV-1.

Okada et teach an immunogenic preparation comprising plasmids pCMV160IIIB expressing HIV *env*, pcREV expressing full length regulatory *rev* and a plasmid encoding and expressing mouse GM-CSF (page 3639 para.3, lines 4--7 and para.4, lines 11-13). Okada et al. do not teach a vaccine comprising a plasmid expressing the gene selected from the group consisting of ORF 1 of PCV -2, ORF 2 of PCV -2, ORF 1 of PCV -1 and ORF 2 of PCV -2.

However at the time the invention was filed, It would have been obvious to one of ordinary skill in the art to make an expression vector expressing the ORFs of porcine circoviruses as taught by Meehan et al. to make an immunogenic composition as taught by Okida et al. One would be motivated to develop a vaccine against a newly identified infectious agent for a disease of economically important farm product.

Claims 2-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meehan et al. and Okada et al. as applied to claims 1and 11 above, and further in view of Felgner et al. (JBC, 1994, Vol.269, No.4, pp.2550-2551).

Claims 2-5 drawn to an immunogenic preparation which has as an adjuvant a cationic lipid, specifically DMRIE, coupled to DOPE.

Okada et al. also teach the immunization of mice with the plasmid mixed with cationic liposomes (page 3639 para.6), consisting of mixture of 3B (N(N' N'-dimethylaminoethane)carbomyl cholesterol(DC-Chol) and Dioeoylphosphatidyl -

ethanolamine (DOPE). In presence of cationic lipids Okada et al. observed higher antibody response (Fig. 2 and Fig.3 ,Fig. 4 and 5, page 3641 para.2 lines 3-6) supporting earlier observation (page 3644, para.2, lines 1-5) with protein immunization in presence of cationic lipids.

Meehan et al. and Okada et al did not teach use of DMRIE and DOPE as adjuvant for the vaccination of mice with HIV-*env* or with ORFs of PCV.

However at the time the invention was made, Felgner et al. study *in vitro* DNA delivery using novel compounds having a hydoxyl moiety on quaternary amine (page 2552, Fig.1) for liposome preparations. They observed that the transfection ability of the lipids were greatly reduced with the increasing chain length from 14 to 18 carbon in saturated series (page 2560, para.1). They also teach transfection with DMRIE/DOPE and observed that over broad range of conditions this composition gave them best results (page 2555, para.1, lines 10-13 and Fig. 4).

In view of the enhanced immune response with DNA vaccines in presence of cationic lipids observed by Okida et al. and the enhanced transfer of DNA to cells in presence of DMRIE/DOPE reported by Felnger et al. it would have been obvious to a person of ordinary skills to change the cationic lipid composition of Okada et al. to the DMRIE/DOPE composition for efficient DNA delivery to cell. One would be motivated to do so, because it was well known in the art that antigen concentration influence the immune response.

Claims 7-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meehan et al. and Okada et al. as applied to claims 1 and 11 above, and further in view of Inumaru et al. (Immunology and cell biology, 1995, Vol.73, pp.474-476).

Claims 7-9 are defines the elements capable of increasing the immune response to be a porcine cytokines, specifically GM-CSF expressed by an expression vector.

Meehan et al teach a plasmid expressing, ORF1 and 2 of PCV-1 and PCv-2. Okada et teach an immunogenic preparation comprising plasmids pCMV160IIIB expressing HIV *env*, pcREV expressing full length regulatory *rev* and a plasmid encoding and expressing mouse GM-CSF (page 3639 para.3, lines 4--7 and para.4, lines 11-13). Okada et al. further teach that cytokines, GM-CSF and IL4 individually, enhanced antibody response (Fig. 4 and 5, page 3641 para.2 lines 9-11). They also teach that CTL response is enhanced when plasmids expressing both GM-CSF and IL-12 both are present in the vaccine preparation (Fig. 6).

Okada et al. do not teach a DNA vaccine for wasting syndromes in pig, comprising plasmids expressing ORF1 and 2 of PCV-2 and PCV-1 with and expression plasmid expressing porcine GM-CSF.

However at the time of the instant invention, Inumaru et al. described the c-DNA clone of porcine GM-CSF. They also show that the overall identity of porcine cDNA with ovine, bovine, human and murine cDNA is 89,86,83 and 70%, respectively. Though, the identity between the GM-CSF from various species is high the biological activity is species specific (Immure et al. pp. 474, para.1, 16-18).

In view of the enhanced immune response observed by Okada et al. for DNA vaccine in presence of GM-CSF and the species specificity of GM-CSF for biological activity, it would have been obvious for one of ordinary skill in the art to make a vaccine preparation for wasting syndrome of pig, comprising a plasmids expressing ORF1 and ORF 2 of PCV together with porcine GM-CSF expression plasmid. The motivation is provided by Okada et al. (pp.3641, para.2, lines10-12) to prepare the claimed invention for protection of economically important farm animal.

Claim10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Okada et al. and Meehan et al. as applied to claims 1 above, and further in view of Felgner et al. and Mumford et al.

Claim 10 is drawn to an immunogenic preparation or vaccine according to claim 1, further characterized in that the element capable of increasing immune response comprises a porcine cytokine and compound selected from the group comprising a porcine cytokine and a compound selected from the group comprising DMRIE, DMRIE/DOPE and carbomer.

As discussed above for claim 1, Meehan et al teach a plasmid expressing, ORF1 and 2 of PCV-1 and PCv-2 and Okada et al. teach co-administration of a vaccine comprising plasmids encoding HIV *env*, HIV rev and a plasmid expressing mouse GM-CSF as a cationic lipid preparation. They demonstrate the role of GM-CSF and cationic lipids in increasing immune response in the vaccinated mice (Fig. 4 and 5, page 3641 para.2 lines 9-11 and Fig. 6) and further demonstrate that cationic lipids gave higher antibody response (Fig. 2 and Fig.3 ,Fig. 4 and 5, page 3641 para.2 lines 3-6). Felgner

et al. teach use of DMRIE/DOPE, cationic lipids for the efficient delivery of the DNA over the broad range of DNA transfection conditions (page 2555, para.1, lines 10-13 and Fig. 4) and Mumford teach use of carbomer as adjuvant for influenza vaccine (page 434,para.4 lines 1-4, and abstract).

It would have been obvious for one of ordinary skill in the art to modify the technique of Okada et al., to make a vaccine for PCV infection by administrating a vaccine comprising expression plasmids for ORF 1 and 2 of PCV -1, mix with cationic lipids of Felgner et al. for enhance delivery and for enhance immune response as observed by Okada et al. Furthermore it would have been obvious to add a plasmid expressing porcine GM-CSF to improve the immune response as taught by Okada et al.

One would be motivated to prepare the claimed invention because one would have recognized that the expression of cytokine together with another adjuvant like lipids and GM-CSF in the vaccine preparation would generate a better and longer lasting immune response. One would have done so because it is art recognized fact that DNA vaccine generate both humoral and immune response and the cationic lipids and GM-CSF enhance the immune response in an animal. Furthermore one would be motivated to generate a vaccine for a newly identified agent for porcine wasting disease.

Claim 6 is free of art.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bharati R. Dhruva whose telephone number is (703) 308-1157. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda can be reached on (703)-305-6608. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Question of formal matters can be directed to the patent analyst Pasty Zimmerman, whose phone number is (703) 305-2758.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703)-308-0196.

brd
April 9, 2001

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